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GUEST EDITORIAL

Locoregional Techniques in the Treatment of Hepatic Tumors

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Cancer of the liver is one of the world's most common malignancies. In Asia, Africa, and India, hepatocellular carcinoma (HCC) is the common liver tumor responsible for at least 250,000 deaths annually [1]. In the United States and Europe, the most common liver cancers are metastatic lesions, most often from the gastrointestinal tract, and of this group of organs, most likely from the colon and rectum. There are 138,000 new cases of colon and rectum cancer in the United States annually [2], and of these cases, one-third eventually die of metastatic cancer of the liver. However, HCC is said to be rare in the West—<6,000 cases in the United States [3] per year—and colon cancer is rare in Africa and the near and far East.

Attempts to resect cancers of the liver progressed slowly in the first part of the twentieth century. Mortalities as high as 50% for right lobe resection were reported as late as 1968 [4]. The risk of operation has dropped rapidly, however, with mortality rates of 2–4% being reported in recent years [5]. As operative risk decreased, large series of hepatic resections, including lobectomies, segmental resections, and nonanatomical resections, were reported for both HCC and metastatic colon cancer from a number of institutions.

The introduction and refinement of CT scans also had an impact on the treatment of hepatic tumors. At one time, such lesions had attained considerable size before they could be diagnosed clinically. CT scans have permitted the discovery of solitary nodules 2 cm or less in diameter. In the early days of liver resection for HCC, disease-free survival at 3 years was only 20%. With the arrival of CT scans and the treatment of selected nodules of 2 cm or less by resection, disease-free survival of 3 years was 53%, but at 5 years it was 30% and at nine years 20% [6]. This shift in the survival curves for the resection of smaller lesions could, arguably, be due to earlier treatment such that it took a longer time to achieve the same result.

Some of the same questions have been raised concerning metastatic colorectal cancer in the liver. Mortality and morbidity rates have improved dramatically following liver resection for this entity. Early diagnosis has continued to improve with new diagnostic techniques. Prognosis is dependent on number and size of metastasis as well as the latent period before the metastatic lesions appear after the primary resection. In selected lesions, 5-year survival following resection is 25–30%. However, many of these results may reflect the natural history of the tumor rather than the effectiveness of the intervention. Silen [7] has entitled one of his reports: ''Hepatic resection for metastasis from colorectal carcinoma is of dubious value.'' He argues in effect that much of the success of resection for metastatic cancer may be due to selection of slow-growing lesions. Silen's work was printed together with a rebuttal by Adson [8], who argued that there is a small but definable group of patients with colorectal hepatic metastasis who can obtain a curative resection.

The natural history of HCC [9] timed from the initial increase in α-fetoprotein suggests that tumors take a mean of 10 months to grow to a diameter of 3.5 cm. At this time, the lesion is still asymptomatic. From this subclinical stage to the appearance of signs and symptoms takes 8 months and a tumor of ~9 cm in diameter. From this to a late stage with jaundice ascites and distant metastasis takes 4 months; median tumor diameter by then is 10 cm. From this stage to death takes 2 months. Thus the median natural course is 24 months. Rate of growth varies tremendously, however, with tumors taking from 10 months to 11 years to reach 10 cm. There is a marked tendency for these tumors to invade branches of the portal veins and to embolize to other parts of the liver. HCC tends to appear in cirrhotic livers; 70–80% of patients with HCC have cirrhosis, many so severe that any hepatic resection is prohibited.

Colorectal metastasis to the liver have a natural history

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TABLE I. Hepatic Cancer Therapy by Nonresectional Techniques

1. Hepatic artery ligation
2. Hepatic artery infusion
   a. Alcohol
   b. Cisplatin
   c. Epirubicin
   d. Mitomycin C
   e. 5-Fluorouridine
   f. Fluxuridine (FUDR)
   g. Levamasol
   h. Leukovorum
   i. Lipidol
3. Intralesional percutaneous alcohol
4. Cryotherapy
5. Hyperthermia
6. Chemoradiation
7. Immunotherapy
8. Biological response modifiers
9. Cytokines
10. Gene therapy

marked by substantial variation in growth. Some poorly differentiated lesions grow very rapidly. Some better differentiated cancers grow very slowly. Nevertheless, long-term survival of untreated patients with liver metastasis is very rare. In a collected series of untreated patients with liver metastasis, mean survival was 4.5–6.6 months. Only 3–4% were alive at 3 years and 1% at 5 years [10]. It is estimated that only 20% of patients with colorectal cancers that have metastasized have cancer limited to the liver alone. Steele and Ravikumar [11] estimate that in the United States, no more than 5,000 patients annually would be eligible for liver resection to remove metastatic disease. At present rates, this would produce ~1,000–1,500 five year survivors, if all patients with metastatic disease limited to the liver were selected for resection. This explains why attempts to cure patients not selected for resection with locoregional techniques usually fail. These patients with large or multiple lesions are the ones most likely to have spread outside the liver. The extrahepatic lesions lead to the death of the patients even when control of the hepatic lesions is achieved. It is for these reasons also that liver transplantation is unsuccessful, except in certain infrequent histological types such as apudomas and hemangio-endotheliomas and has been abandoned [12].

An arsenal of physical, chemical, and rheological agents have recently emerged (for a partial list see Table I) either to reduce the volume of hepatic tumors and make them more operable or to avoid recurrences or as alternatives to resection. These agents include embolization of the arterial tree to cause ischemia in the tumors. In embolization with lipiodal in hepatocellular tumors, lipiodal is preferentially absorbed by the tumors and can be used as a carrier for chemotherapeutic or radioactive substances. Chemotherapeutic injection of the involved liver can be followed by arterial embolization with absorbent materials such as gel foam, causing the chemotherapeutic agents to accumulate at high concentrations behind the obstruction. Alcohol injections given percutaneously have been used in hepatocellular cancer. Alcohol also has been given intra-arterially following embolization of a hepatic segment. Cold and heat have been applied to both hepatocellular and metastatic cancers. The cavitron, an ultrasonic device, has been used to resect scattered lesions of the liver nonanatomically. All of these agents, in various combinations or alone, have been proposed for use as therapeutic adjuvants, prophylactic, and palliative agents [13]. The possible combinations of so many different techniques will be particularly difficult to sort out.

Most of the current studies are retrospective. The majority of studies concerning hepatocellular carcinoma (HCC) come from Japan, Taiwan, and China. Studies concerning colorectal cancer metastases come mainly from the United States and Europe. Tang et al. [14] reported on 663 patients with HCC, found unresectable at operation and then treated with a variety of techniques. Seventy-two patients (11%) had their tumors reduced to a resectable size. Elias et al. [15], reporting from the Institut Gustave Roussy in France, remarked on 14 cases (5.8%) of 239 patients who received prolonged intra-arterial infusion chemotherapy and had a substantial regression of previously inoperable lesions leading to successful hepatectomy, Kotoh et al. [16] have reported that patients with small, solitary hepatocellular carcinoma treated by ultrasound guided injections of 95% alcohol do just as well as patients with similar lesions treated by resection. Patients in this study were not randomized, but selected by liver function. Those receiving alcohol injections had substantially poorer hepatic function than those who received operation. Neither group did particularly well since all but three of 23 patients who received ethanol injections died or were alive with recurrences. Of the 17 patients who had operations, one died postoperatively and all but three had recurrences.

Horiguchi et al. [17] screened patients with ultrasonography, CT, and MRI to detect HCC <3 cm, but found that only 12% of these patients were candidates for resection because of advanced cirrhosis. Treatment of small lesions 1.5 cm or less by either percutaneous alcohol (PA) to transarterial chemoembolization (TACE) gave similar results with 80% survival at 3 years. For lesions 1.6–3 cm in diameter, PA seemed superior with 70% 4-year survival compared to 45%. However, prospective randomized studies comparing these therapies are rare. It is noteworthy that in one recent randomized study, patients receiving TACE fared no better than patients treated symptomatically [18]. Since the liver of patients with HCC is so often severely damaged by preexisting cirrhosis, it is tempting to solve both the problems of cirrhosis and malignancy by liver transplantation.

However, obtaining donor livers is so difficult that such treatment should be reserved for patients with the best chance of success. Schwartz et al. [19] reported that patients with HCC 5 cm or less had no tumor recurrences after transplantation. Bismuth and Chiche [20] compared resection for HCC with transplantation. There were 60 patients in each group. Survival without recurrence was significantly better in the transplant group at 3 years (23% vs. 44%). The best results (83% survival without recurrence at 3 years) were patients treated by transplantation for nodules of <3 cm.

Locoregional techniques of therapy are less likely to help patients that have colorectal metastasis to the liver since the great majority will have accompanying spread to other organs. Such patients with be helped only when we discover effective adjuvant systemic therapy. We still believe that the surgical oncologist should search carefully for the occasional patient who may benefit from resection. As Steele [11] has pointed out, if the criteria for resection are strict enough, we may operate on fewer patients but the percentage who will benefit can be increased. In a recent presentation before the American Surgical Association, Bismuth and his co-workers [12] reported on the treatment of 337 patients with chemotherapy (5-fluorouridine, folinic acid, and oxaliplatinum) successfully downstaging 53 (16%) to make them operable. Survival in their group was 39% at 5 years.

HCC may be better served by locoregional techniques of treatment since it is a primary, not a secondary, lesion and spread outside the liver is a sequential, not a simultaneous, event. Moreover, distant spread from the liver is less common in HCC. Retrospective studies of a large number of different locoregional treatments have been done. What is needed now are prospective randomized trials. The large pools of patients with HCC in relatively advanced countries such as Japan, Taiwan, Korea, South Africa, as well as China and India should offer ample opportunities for significant studies.

In summary, primary or secondary cancers of the liver are a major global problem. A large number of locoregional treatments of HCC have been proposed. Appropriate prospective randomized trials of these treatments are needed and must be done in countries where HCC is common. Locoregional treatments are less likely to help patients with secondary cancers of the liver such as metastatic colorectal cancer. Treatments of the liver lesions may be successful, but many patients will die of metastatic disease elsewhere. More successful treatment of patients with colorectal lesions awaits effective systemic therapy.

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